CLINICAL CONFERENCE

Treatment of Diarrhea in the Infant

A condensed report of the presentation made by Doctors Paul Freeman, John Castiglione, Alfred Fisher, and Paul Betzold at a staff conference at Children's Hospital of the East Bay, Oakland, California, May 6, 1947. Service of Dr. Clifford Sweet.

DR. PAUL FREEMAN: In the past few years there has been a vast increase in the knowledge of metabolic disturbances incident to dehydration and starvation. The increased availability of various fluids and specific nutrients concerned in the treatment of such disorders has resulted in more successful therapeutic measures, and has increased the responsibility of the physician in the administration of fluids. Our purpose here is to very briefly outline the available data on the proper use of parenteral fluids.

An estimate of the maintenance requirements of the resting child is an obvious prerequisite to the logical use of parenteral fluids in the sick child, and in Charts 1 and 2 we have represented the daily maintenance requirements of water, salt, calories, and protein, for resting infants and children. Note that the infant's water loss is about five times that of the adult's per unit of body weight.

CHART 1.—*Water Loss of the Resting Child*

Size	Total Loss	Usual Water Allowance
Infants	300 to 840 cc.	300 to 1000 cc. (60 cc/lb.)
Children, 20-80 lbs.	840 to 1500 cc.	1000 to 1800 cc. (35-45 cc/lb.)
Adults, 140 lbs.	1500 to 2100 cc.	1800 to 2500 cc. (20-25 cc/lb.)

It is just as important to see that these allowances are not grossly exceeded as it is to see that they are met, especially with respect to sodium chloride. A glance at the charts will show that if all the daily water requirements were given as normal saline solution, the salt requirements would be exceeded by some 500 per cent, which would result in harmful retention, generalized edema, and a decrease in urinary volume. This oliguria might be interpreted by the unwary physician as an indication for more fluids, as a sign of circulatory failure or renal insufficiency, or, if the patient were receiving a sulfonamide, as a sulfonamide oliguria. This latter interpretation might result in the discontinuance of a needed drug, or if the drug were continued, might indeed result in needless hematuria because of the oliguria. For these important reasons, the daily maintenance requirements of sodium chloride should not be greatly exceeded.

As in the past, the daily caloric requirements are supplied by dextrose parenterally, and, in such administration, the dextrose has reduced the endogenous protein catabolism to a minimum, thus acting as a body-protein-sparing agent. Today we can supply at least the basic protein requirements by the addition of amino acids to the parenteral fluids. Enzymatic hydrolysates of casein and pancreatic tissue which supply all ten of the essential amino acids have been available commercially for some time. If such a preparation is used, the concentration in the infusion should not exceed 5 per cent, since too rapid administration may result in vomiting hyperpyrexia, polyuria, and venous thrombosis. However, these amino acid preparations have not replaced blood and plasma as a means of supplying the daily protein requirements, and in the presence of anemia whole blood is specificially indicated. If hemoconcentration exists, plasma should be used to furnish the protein.

From Charts 1 and 2 the needs of the infant in terms of water, calories, salt and protein can be calculated. It is not possible to supply the maintenance needs as outlined here by clysis or by short intravenous infusions and clyses. A continuous intravenous drip is the method which should be used, and the rate of infusion should be limited by the ability of the child to oxidize the dextrose. This has been shown to be about 4 cc. of 10 per cent dextrose solution per pound per hour. Solutions given in excess of this rate produce a significant hyperglycemia and glycosuria, which of themselves have a dehydration effect, and may in addition exert a deleterious effect upon the kidneys and pancreas.[4] Whole blood or plasma transfusions at frequent intervals during the course of the parenteral therapy are required to supplement such fluids, and since whole blood supports blood and plasma volume better than plasma, it should be used unless there is a specific contraindication.

Up to this point we have been discussing the *maintenance needs* of the patients who are unable to take

CHART 2.—*Daily Basal Maintenance Requirements of Calories, Salt, Protein*

Size	Caloric (Gm. dextrose)	Amino Acids*	Salt (Normal Saline)†
Young infants	30 Cal/lb. or 7.5 Gm/lb.	0.75 Gm/lb.	1 Gm. or 125 cc. N.S.S.
Older infants	28 Cal/lb. or 6.5 Gm/lb.	0.5 Gm/lb.	1 Gm. or 125 cc. N.S.S.
Children	15 Cal/lb. or 3.5 Gm/lb.	0.3 Gm/lb.	80 cc., plus 2½ cc/lb. N.S.S.

* Blood and plasma are considered 5 per cent protein, or 5 Gm. per 100 cc.
† Blood and plasma are considered to be half normal saline solution, i.e., 100 cc. supplies 0.45 Gm. salt.
† Lactate-Ringer's solution contains 0.6 Gm. sodium chloride per 100 cc.

oral feedings. Such patients, when first seen, are usually suffering from starvation and dehydration; therefore, an estimate of the *amount* and *quality* of their fluid losses must be made and appropriate repair needs provided parenterally *in addition* to their maintenance requirements. The most reliable method for determining the amount and quality of loss of body fluids is by a careful history and clinical appraisal, evaluating particularly the length and severity of fluid loss by diarrhea or vomiting, the weight loss, tissue hydration and urine volume and concentration. Laboratory confirmation of the clinical impression is desirable, the hemoglobin, hematocrit, blood proteins, chlorides, and carbon dioxide combining power being especially useful.

Since for practical purposes all of the weight loss sustained by a dehydrated, starved patient is simple loss of water, this entire weight loss as estimated by the physician should be replaced with 24 hours of hospital admission by appropriate parenteral fluids. In addition, the maintenance needs for this period must also be met.

In Chart 3 is presented an assumed problem of a dehydrated acidotic infant of 5 kilograms and shows his approximate parenteral needs over and above his maintenance requirements. Had this child been a dehydrated alkalotic patient (with, for example, pyloric stenosis) the extracellular fluid losses would have been replaced with normal saline solution because of the need for a higher concentration of chloride ions. The two solutions which are recommended as physiologically most suited for the repair needs of the extracellular fluids are (1) normal saline solution in cases of alkalosis, and (2) a combination of one part sixth molar sodium lactate with two parts normal saline solution for cases of acidosis. It should be remembered that normal saline solution is hypertonic with respect to the chloride ion of the blood.

CHART 3.—*Calculation of Needs of a Dehydrated 5 Kilogram (11 Pound) Infant*

*Fluid Loss: Estimated:**	
1. Weight before dehydration	5000 Gm.
2. Weight after dehydration	4400 Gm.
3. Total loss or 600 cc. water	600 Gm.
4. Extracellular fluid loss (½ of total)	300 cc.
5. Intracellular fluid loss (½ of total)	300 cc.
Provision For Replacement:	
1. Mixture of 1 part sixth molar sodium lactate and two parts normal saline for extracellulor fluid loss	300 cc.
2. Serum for protein depletion	100 cc.
3. Blood for Hgb. and protein depletion	100 cc.

* Where weight prior to dehydration is not known, replacement may be undertaken by the following estimation: for severe dehydration, 10 per cent of body weight should be replaced; for mild dehydration 5 per cent of body weight should be replaced.

Three points presented here we feel to be worthy of special emphasis:

1. The injudicious use of excessive amounts of normal saline solution in attempting to hydrate a patient may quickly lead to water retention.

2. Too rapid administration of dextrose, if long continued, may result in harmful glycosuria, hyperglycemia, and diuresis.

3. The most complete parenteral fluids available today are inadequate with respect to certain intracellular needs, and the necessity of initiating oral feedings as soon as possible must be clearly borne in mind. (The source of the material in this discussion and in the charts presented is largely the work of Butler and Talbot of Boston.[1])

CASE PRESENTATION

DR. CASTIGLIONE: With the introduction afforded by Dr. Freeman's discussion, I wish to present the case of a child in whom we feel that the maintenance of hydration by parenteral therapy was inadequately controlled.

A five months old infant was first admitted to the wards of Children's Hospital on February 11, 1947. The history was of an upper respiratory infection of three days' duration which had become complicated by deep cough, diarrhea, and fever of 106 degrees. Treatment was directed initially at the diagnosed bronchopneumonia and otitis media, and the diarrhea subsided almost immediately. Antibiotic therapy was successful, and the child gradually improved. On the 14th hospital day a complicating hemolytic staphylococcal pyelonephritis caused a rise in temperature and a few loose bowel movements, but this urinary infection was controlled by sulfadiazine. The patient was discharged as improved on the 20th hospital day. She had lost a total of 1 pound 9 ounces during hospitalization.

Three days following discharge she was returned to the hospital with the story of having had 22 large watery stools in the preceding 24 hours. She had vomited twice and had been extremely listless. The temperature on entry was 103.6 degrees. Weight was 12 pounds 12 ounces. Examination revealed a limp, unresponsive, extremely toxic baby, with a distended, tympanitic abdomen. No evidence of parenteral infection was found. An infusion and a clysis were given immediately and oral feedings were started in 12 hours because no diarrhea had been noted. All feedings were immediately vomited, however, and diarrhea again resumed.

Intravenous alimentation was begun and sulfadiazine and penicillin given. At first there was some improvement in the extreme toxicity, but a hectic febrile course started on the third hospital day, with spikes of fever to 105 or 106 degrees, and the baby expired on the ninth hospital day, the 35th day since onset of illness. Bowel movements were not exceedingly frequent, numbering three to four per day, but they were massive in volume.

Laboratory work revealed little of significance. An initial leukocytosis subsided by the seventh day. Hemoconcentration of 18 Gm. Hgb. on entry had fallen to 9 Gm. by the sixth day, and transfusions were given. Blood, urine and stool cultures were negative, and blood sugars were normal.

Postmortem examination was complete, but revealed only the following significant findings:

1. Acute catarrhal enteritis with agonal intussuseptions.
2. Generalized anasarca.

Because of the severe persistent toxemia and hyperpyrexia, the continued downhill course of this patient led to the fatal outcome. It was a shock to us, however, to find at postmortem the marked anasarca, with serous fluid in all body cavities. We therefore set out to review our treatment and to determine, if possible, the sources of our errors in the application of the principles of parenteral therapy.

We first recalculated the fluid and salt requirements, using the method outlined by Dodd and Rappaport[2] in their discussion of parenteral alimentation of infants with diarrhea. By their standards (which were modified from those figures determined by Talbot and Butler) the estimates of fluid need shown in Chart 4 were derived. The actual fluid that the baby received is indicated on Chart 5.

A review of these data makes more apparent certain errors of treatment:

1. Initial failure to evaluate the infant properly and to make up her replacement fluid needs; and, throughout the period of hospitalization, administration of an excess of saline and total fluid.

2. The choice of types and amounts of parenteral fluids was based upon clinical appraisal of the patient, without use of serial laboratory measurements to check the blood chloride, the state of hydration, and the acid-base balance of the infant. (Dodd has emphasized the unreliability of clinical judgment alone in estimating mineral losses in diarrheal states.[2])

3. The use of continuous intravenous infusion through a cut-down needle necessitated the administration of fluids for 24 hours a day. This led unwittingly on several occasions to giving too great a volume of fluid through inability to control the rate of flow accurately enough.

4. The caloric needs were not completely covered by glucose. Thus the amino acids administered were of necessity utilized for energy by the child rather than as building-stones for body repair processes.

The massive accumulation of water and salt that we found in all tissues at postmortem was, in part at least, the result of these errors. To avoid such mistakes in the future, we have agreed upon the following measures in our treatment of dehydration.

1. For all patients for whom we feel more than minimal parenteral administration of fluids is indicated, careful calculation of basic and replacement need, using such figures as we have presented here, will precede the inauguration of therapy.

2. More frequent use will be made of laboratory procedures in confirming or altering our clinical impressions as to state of hydration, with special reference to the amount of salt required.

3. We are developing a technique of utilizing continuous intravenous infusions into the scalp veins of infants. In this way we hope to meet the daily fluid requirements within a period of 18 hours, thus allowing the child intervals free of restraints when he can have full activity and during which time he can be weighed and bathed. This will obviate the round-the-clock need for fluid administration in order to keep a cut-down needle clear.

4. A system of charting the fluids administered, modified after Dodd, is being used and is proving an excellent means of careful daily control of our parenteral therapy.

While we do not believe that our errors in the care of this patient were primarily responsible for her death, we do feel that the analysis of our handling of her has been of great value to us, and we have presented her case here in an effort to share what we believe to be important considerations in the treatment of diarrhea in infants and children.

DR. HOROWITZ: Our residents here do not have all failures. They have had many successful cases. One for which the House Staff may take much credit will be presented by Dr. Betzold.

CASE PRESENTATION

DR. BETZOLD: An eight-day-old female entered the hospital January 3, 1947, having been born on Christmas of 1946 after a seven-month gestation, with a birth weight of 4 pounds, 10 ounces. The history prior to admission was only: "The child vomited on several occasions. The reason for transfer is lack of room at the referring hospital." The family history was non-contributory. Physical examination revealed a 3 pound, 12 ounce infant who was described as "looking as though it were hung together with strings." The baby was active, with a good cry, and responded vigorously to stimulation. No positive findings were noted save for irregular respirations, with shallow breaths followed by deep sighing respirations. The routine blood and urine tests were normal,

CHART 4.—*Basic Maintenance Requirements of a 13 Pound Infant*

	Basal Need	Replacement	Total
SALT	1 Gm. NaCl or 125 cc. normal saline sol. or 160 cc. lactate Ringer's sol. or 250 cc. blood, plasma.	5% of 13# or 350 cc. salt-containing fluid as N.S.S.	125 cc. normal saline solution daily. 475 cc. salt-containing fluid 1st day as N.S.S.
CALORIES	20 Cal/lb. or 5 Gm. glucose/lb. or 1300 cc. 5% glucose or 650 cc. 10% glucose.	None unless additional needed to combat acidosis.	650 cc. 10% glucose or 1300 cc. 5% glucose.
PROTEIN	1 Gm/lb. or 100 cc. 15% amino acid sol. or 300 cc. blood, plasma.	⅓ to ½ of salt-containing fluid for replacement should be blood or plasma.	300 cc. blood, plasma, or amino acid sol. daily; 250 cc. blood or plasma 1st 24 hr. as part of salt replacement.
FLUID	60 cc/lb. or 800 cc. daily.	See SALT, PROTEIN.	1375 cc. 1st day, 800 cc. daily thereafter.

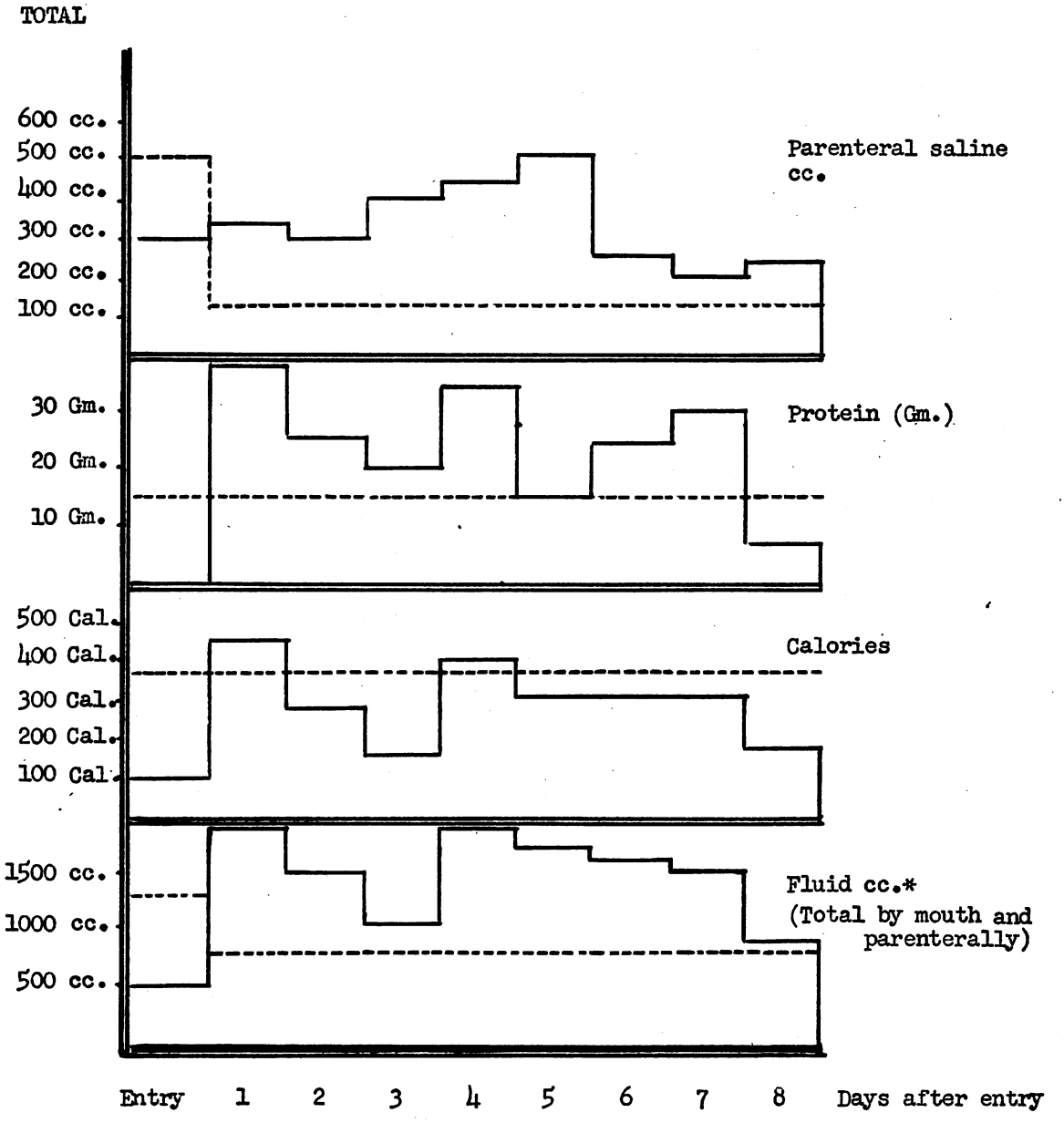
SUMMARY: First 24 hr. 250 cc. plasma.
350 cc. 10% glucose in normal saline sol.
650 cc. 10% glucose in water.

Daily thereafter:
125 cc. normal saline sol. mixed with
100 cc. 15% amino acid sol. mixed with
650 cc. 10% glucose in water.

To be given at rate of 60 cc. per hour over 15 hrs/day.

and the Kahn was negative. Routine premature care was established, and for four days the infant gained well to 4 pounds, 1½ ounces. It then developed a diarrhea, with weight loss, dehydration, weakness and debility despite transfusions, parenteral protein therapy, vitamins, clyses, and general supportive measures. A persistent dusky cyanosis developed which was not helped by oxygen, and a greyish pigmentation of the skin was reported. At four o'clock on the morning of February 10 a progress note was written. It describes the infant as follows: "Respirations irregular, color poor, slow jerking movements of head and extremities. Thighs, vulva, and lower abdomen distended with clysis fluid. Color improved by oxygen but still dusky. Has had one loose yellow stool during the night. Impression: diarrhea with toxic manifestation, uncontrolled." At this time calcium gluconate was administered intravenously to combat the convulsions, and the condition of the child improved. Later that day the blood sugar was recorded as 43 mgm. per cent. Because of the low blood sugar, desoxycorticosterone acetate therapy was begun with an initial dose of 2.0 mgm. and then 0.5 mgm. daily. From this time the progress notes indicate continuous improvement in the child's condition. The diarrhea subsided,

CHART 5.—*The Broken Lines Indicate the Calculated Requirements and the Dark Lines the Actual Amounts the Baby Received*



* Note that Dodd and Rappaport set no upper limit of total fluid administration, but restrict carefully the salt intake.

respirations became stronger, the hydration improved, and the child began to eat better. A gain in weight accrued gradually at first, more rapidly later, and despite a few episodes of mild diarrhea, there was continuous gain in weight and increase in strength. Blood sugar on February 25 was 83 mgm. per cent. On March 3, the cortical hormone dosage was reduced to 0.5 mgm. every other day and was discontinued on discharge, April 5, when the baby weighed 6 pounds, 4 ounces.

Three weeks later the child was seen. She weighed 8 pounds, 6 ounces and was a well-nourished child with no evidence of disease. Hydration was excellent, with a good layer of subcutaneous fat. The mother stated that the baby was active and well.

Dr. Fisher, who followed this case, and whose name appears frequently on the chart, will discuss it in relation to the use of the adrenal cortical hormone in diarrheal disease.

DR. FISHER: The problem of the newborn who develops diarrhea without apparent cause shortly after dismissal from the hospital, who fails to become hydrated despite adequate parenteral therapy, who refuses to take more than one or one and a half ounces each feeding (and may even throw up a good part of that), and whose weight steadily decreases, constitutes a perennial problem to the pediatrician.

In the December, 1946, Journal of Pediatrics, Dr. J. C. Jaudon[3] reported a series of nine cases in which findings were similar; namely, general debility and weakness, appearance of impending shock, and a marked tendency to dehydration despite adequate parenteral fluid therapy. All were cases showing little hope of recovery, and in which any form of therapy seemed justifiable, regardless of its drastic character. Several of the infants showed blood sugar values between 10 and 20 mgm. per cent. Four patients had anorexia and loose stools from the early days of life without evidence of infection. Two others developed diarrhea in association with a staphylococcus septicemia, the latter responding well to penicillin therapy, but the loose stools and downward course persisted until adequate therapy was instituted.

The solution to these problems seems to be adrenal cortical hormone which produced such dramatic results in Jaudon's series and certainly aided our patient. In explaining the rationale of this therapy, Jaudon points to the anatomical structure of the adrenal gland during intrauterine life—the gland being composed primarily of fetal cortex or androgenic zone, with only a small rim of closely packed cells, the true cortex, forming a sheath about the others. Immediately following birth, the androgenic zone begins a rapid involution, while the rim of the true cortex commences to enlarge, probably due to an increased demand for its secretion. The question is posed, "Could there not be a phase of physiologically low activity during the period of transition?" If true, this concept would explain some of the deaths of premature and newborn infants in the first few weeks of life, which are preceded by periods of prolonged unexplained debility not responding to therapy. It would also shed some light on the course of certain infants who fail to rally despite the eradication of the disease which initiated the disability. McKittrick[6] and Ketteringham[5] have shown that almost all infants display a physiological hypoglycemia during the first few days of life which might be interpreted as a disturbance of carbohydrate metabolism secondary to low adrenal function. The rapidity with which glycogen disappears from the newborn liver also suggests adrenal hypofunction.

Each of Jaudon's infants received adrenal cortical hormone either as extract of beef or pig adrenal or as the synthetic desoxycorticosterone acetate, although all ended up on gradually decreasing doses of the latter. Dosage ranged from 0.5 to 5.0 mgm. of synthetic preparation, depending upon the physiological response. With recovery, the dosage was gradually reduced over a period of three to four weeks. All infants save one one were returned home completely weaned from the drug.

Jaudon makes a strong plea against the indiscriminate use of the hormone in large dosages, as it is far from innocuous. In combination with a large intake of sodium chloride, it has been shown experimentally to produce degenerative lesions in the arterioles of the brain, kidney and heart. In addition, it is theoretically possible to cause permanent atrophy of the adrenal cortex by prolonged or unwarranted administration of the hormone. This was exemplified by one case in this series who required a daily maintenance dose following administration for several months.

In summary, may I point out the signs of adrenal insufficiency in infancy, as corroborated by animal experimentation: a pronounced tendency to dehydration, asthenia, weight loss, hypoglycemia, anorexia, intermittent vomiting, loose stools, and failure to gain weight. The newborn infant who manifests any or all of these signs, without apparent reason, or the ailing child whose bacteria have been eliminated but who still fails to rally, must be strongly suspect of adrenal cortex insufficiency and the diagnosis subjected to laboratory confirmation. The blood sugar will probably be low, as well as the blood sodium and chloride; while the potassium level usually will be high. With this laboratory confirmation, daily intramuscular injections of adrenal cortical hormone (natural, or synthetic in the form of desoxycorticosterone acetate, 0.5 to 5.0 mgm.) are indicated.

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